THE PRESENT STATUS OF THE THYMUS GLAND IN PÆDIATRIC PRACTICE*

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THERE is probably no organ of the human body which is so enshrouded in mystery as the thymus gland. Its anatomical relationships and its histological structure are well known but we know little about its physiological function and its pathology. This ignorance is reflected in the frequency with which it is cited as the etiological agent in a wide variety of diseases. It is commonly believed to be a cause of sudden death, particularly in infancy, and is still frequently employed as an alibi for an untimely or carelessly given anæsthetic. It is its relationship only to certain clinical manifestations in infancy and childhood which I intend to discuss in this paper.

Ever since the recognition of the gland as an anatomical entity in the first and second century the pendulum of medical thought concerning its importance in the body has swung backward and forward, and never has there been any unanimity of opinion. The functions attributed to it in the 16th, 17th and early part of the 18th century were many, varied, and fanciful. Reports of sudden death due to enlargement of the thymus appeared in the literature as early as 1614, and there were many more in the 18th century. The end of the 18th and beginning of the 19th centuries produced many descriptions of thymic asthma due to pressure of an enlarged gland, and, in Germany particularly, numerous thymectomies were performed with reported benefit. Paltauf's description[1, 2] in 1889-1890 of the condition, which he termed "status thymico-lymphaticus" was the first important contribution to the subject. Next came the era in which experimental proof was adduced that the thymus was a ductless gland with an internal secretion, only to be squashed by equally convincing proof to the contrary. In the last twenty years the controversy has been focussed on the culpability of the gland for the occurrence of sudden fatalities and on its physiological function from an endocrinological point of view.

In order to arrive at a satisfactory conclusion regarding the importance of the thymus it is necessary to answer three main questions. (1) Is there such a pathological entity as status lymphaticus? (2) Does the thymus liberate an internal secretion, and, if so, what is its significance in relation to sudden unexplained deaths in childhood? (3) Is there any real proof that an enlarged gland can produce symptoms by the application of some mechanical force such as pressure or traction?

Status thymico-lymphaticus.—Since Paltauf's original description of this syndrome the only important corroboration has been contributed by Symmers,[3] whose careful work on a large number of autopsies conducted in the Children's Department of Bellevue Hospital deserves consideration.

The important features of the syndrome as described by him were "Certain peculiarities of the body configuration, persistence of the thymus, hyperplasia of lymphoid tissue in the spleen, intestines, and elsewhere, hypoplasia of the vascular system and developmental deficiencies in the genitalia. These anatomical anomalies are attended by instability of all the lymphoid tissue, providing a mechanism which, when set in motion, is capable of so sensitizing the body as to produce anaphylactic phenomena of varying intensity." He also advanced an interesting theory to explain the anaphylactic shock which he believed to be responsible for the sudden fatalities. This theory was, in brief, that symptoms were produced by the sudden release into the system of a nucleo-proteid formed as a result of destruction of innumerable germinal follicles in lymph glands throughout the body.

It is important to note, however, that no other confirmation of this theory has been recently published. The diagnosis of status lymphaticus as a clinical or pathological entity has rapidly fallen into disfavour. In the Hospital for Sick Children such a diagnosis has been made only five times in the last fifteen

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years, and an analysis of the case histories reveals that there was little justification for such a diagnosis. In three instances no autopsy was performed; and the other two were children who were apparently overwhelmed by a severe toxæmia associated with convulsions and a high temperature, and at autopsy no cause was found sufficient to explain death. The thymuses weighed respectively 29 and 39 g. and in both instances there was general glandular enlargement. The conclusion of the Status Lymphaticus Investigation Committee in Great Britain, after an analysis of collected data, was that there was no such pathological entity. In their material there was, curiously enough, no instance of sudden unexplained death in infancy. I am convinced that the confusion which exists concerning status lymphaticus has been caused by the misguided effort to combine several distinct pathological conditions such as lymphadenosis, hypogenitalism, etc., into one syndrome.

Physiological function.—The literature dealing with the possible functions of the thymus gland is so voluminous that it would be impracticable to cover it here. Suffice it to say that in the last six years enough experimental proof has been advanced, mainly by Rowntree and his co-workers,[5-8] to permit the conclusion that the gland is a definite link in the endocrine system. Thymectomy in animals has been shown to produce genital hypoplasia, enlargement of the adrenal cortex, compensatory hypertrophy of the thyroid and retardation of growth in successive generations. X-ray therapy of the thymus in rats has been followed by retardation in development of the gonads. Administration of thymus extract produces in the young of successive generations of rats acceleration of growth and of adolescence, and an increase of fertility rate. Excision of the adrenals in rabbits not only prevents thymic involution but causes hyperplasia of the involuted thymus. Castration in male rabbits is followed by hypertrophy of the thymus, and this same phenomenon has been observed in eunuchs. Actual demonstration or isolation of an internal secretion from the gland has, however, not been forthcoming. Even if it were, it could hardly explain the rapidity with which death occurs in apparently normal infants. There is no parallel for such a phenomenon in the realms of endocrinology.

The relation of an enlarged thymus to sudden death.—The second decade of this century experienced an acute revival of interest in the thymus gland. This was the result of a series of publications which endeavoured to associate the enlarged gland with a certain clinical syndrome which comprised such symptoms as brassy cough, noisy breathing, cyanosis, choking attacks, syncope, and even sudden death. One such publication emanated from the Hospital for Sick Children in 1927, and I was co-author with Dr. Alan Brown and Dr. Rolph. It is interesting, now, to review the events that prompted the paper, the clinical observations on which our conclusions were based, and the gradually increasing realization during the following ten years that many of our cherished convictions were untenable.

In the three or four years before the publication a succession of sudden unexplained deaths of young infants had occurred in this city. A review of the case histories revealed that many of them had had for some months before death certain unexplained and, at times, alarming symptoms. The demonstration at autopsy of an enlarged thymus suggested an etiological relationship. For some years, then, all infants exhibiting these symptoms were given x-ray therapy over the region of the thymus, and the apparent success of this treatment increased the conviction that the enlarged gland was the causative factor. Doubt of the truth of this conviction was a gradual development during the next eight or ten years, and was fostered by several occurrences. Not all the children with suspicious symptoms were relieved by x-ray therapy; many infants with large thymic shadows were symptom-free; and not all those with suggestive signs had demonstrable enlargement. What was even more disturbing was the demonstration that other pathological conditions, notably tetany of the new-born and allergic shock, could produce identical symptoms. Medical thought is still confused but in the last few years the trend has been toward the absolution of the thymus from all blame.

An impartial analysis of the arguments pro and con, as set down below, are enlightening:

A. Observations which favour the theory that the thymus is the causative agent.

1. The firm belief, still held by many clinicians that certain suspicious symptoms in infancy are relieved by irradiation of the thymus.

2. The fact that diminution of the thymic shadow is coincident with this clinical improvement.

3. The reports in the German literature that signs of tracheal pressure have been relieved by thymectomy or thymoprexy. It should be stressed, however, that sufficient care was not used to eliminate the possibility of the enlargement of the gland being due to lymphosarcomatosis.

4. The frequently quoted statement of Chevalier Jackson[13] that compression of the trachea due to a large thymus has been demonstrated by him by bronchoscopic examination. His references to this condition are however casual and vague, giving no figures as to the number of cases observed or any information regarding their ultimate disposition.

5. Accredited experimental evidence that the thymus is linked with other ductless glands, and even, possibly, possesses an internal secretion. That an increase or diminution of such secretion could be the cause of symptoms is however purely conjectural.

B. Arguments tending to disprove the theory.

1. Actual proof that enlargement of the thymus can of itself produce symptoms has never been advanced at any time.

2. There is very considerable evidence that the weight of an enlarged thymus gland is insufficient to produce tracheal compression. Taumassia has shown experimentally that this would require a weight of 180 g. Simple hypertrophy rarely if ever produces this weight. Excepting Chevalier Jackson's observations, there has been no radiological or bronchoscopic confirmation of tracheal compression.

3. There has been, in the past, much misunderstanding as to what constitutes an enlargement of the gland. Different observers report that from 30 to 55 per cent of normal new-born infants have x-ray enlargement. Many statistics designed to show the weight of the thymus at various ages have been based on autopsies performed on subjects who have died after prolonged illness. Under this condition the gland is known to decrease rapidly in size.

4. Many children with suspicious symptoms have normal thymi and vice versa. Many large glands occur in normal symptom-free children.

5. The recognition of tetany of the new-born as a clinical entity has introduced a new etiological factor. Low blood calcium has been proved to be the cause of many of the symptoms formerly attributed to the thymus gland. It is interesting to record in this connection the experimental findings of three observers. Mettenleiter[17] proved that x-raying the thymus caused better utilization of calcium in the body. Eicholz[15] showed that x-ray treatment of any part of the body surface caused elevation of the serum calcium; and Nesbitt[16] described 13 instances of elevation of serum and spinal fluid calcium following x-ray therapy in children with symptoms suggestive of thymic dysfunction. His treatments were not given over the region of the thymus but they *were* followed by cessation of symptoms. It is more than likely that we have in the past been relieving by our x-ray treatment mild cases of tetany of the new-born.

6. Many suspicious symptoms such as noisy nasal breathing, cough, choking attacks and syncope can be satisfactorily explained on an allergic basis. I have, personally, seen a number of infants exhibiting symptoms of all degrees of severity, and have been able to prove to my own satisfaction that the causative factor was sensitization to some foreign protein such as animal fur, feathers, etc. Fifteen years ago I would have, for lack of a better diagnosis, classed them all as thymic disturbances. It is interesting to note that Symmers, in his treatise on status lymphaticus emphasized the allergic manifestations and pointed to the danger of sudden death from allergic shock. Waldbott[18-21] in a series of publications in this connection draws attention to several significant facts. (*a*) The thymus and other lymphatic glands in the body are almost invariably enlarged in the allergic child. This has been described also by Tumpeer. (*b*) In sudden death due to allergic shock, such as occasionally follows injection of horse-serum, the pathological and histological pictures of the organs are identical with that described in so-called thymic death. (*c*) A family history of allergy is found very frequently in infants exhibiting suspicious thymic symptoms. This observation I can confirm from many observations of my own. It is interesting to recall that in our original paper on this subject in 1927 we drew attention to the fact that 22 per cent of the patients were suffering from eczema. (*d*) Waldbott reported, also, five proved instances of allergy to anæsthetics such as ether, novocaine, etc. Here then is an adequate explanation for the rare anæsthetic fatality where other factors such as

aspiration of stomach contents or mucus have been excluded.

7. Other well recognized causative factors in the production of cyanosis of the new-born and even of sudden death in infants are often ignored or minimized, in an effort to forestall misdirected criticism of the obstetrician or the infant's parent or nurse. Aspiration of mucus, with or without demonstrable atelectasis, is undoubtedly the most frequent cause of cyanosis of the new-born, and suffocation due to inhalation of vomitus or overlying by the mother during sleep is a not infrequent cause of death in normal infants.

8. The etiological relationship between the thymus gland and holding-breath spasms is very questionable. A much more logical explanation of the phenomenon would be that vigorous crying washes the CO_2 out of the blood, producing a period of apnœa and unconsciousness.

A critical review of the above arguments pro and con reveals that the case for the thymus rests on very scanty evidence, and that the most convincing argument against the gland rests in the fact that most of the suspicious symptoms can be much more logically and scientifically explained by other known pathological processes. There are still some symptoms for which there is no adequate explanation. We all encounter, for example, the two-year old child who, following a slight injury, becomes blue and unconscious, and who remains in a state of semi-stupor for several minutes. This type of attack is not helped by x-ray therapy, and I believe there is no relation between it and the thymus. So long, however, as the medical profession persists in attributing this symptom, and similar ones, to some fanciful dysfunction of the gland, so long will scientific investigation and clinical observation be hampered in their efforts to discover the true cause and the proper remedy.

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THE COMPARATIVE VALUE OF VARIOUS TUBERCULIN TESTS IN CHILDREN, MEDICAL STUDENTS, AND NURSES-IN-TRAINING*

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UNTIL quite recently a positive tuberculin reaction in the adult was considered to be almost universal, and, therefore, of little clinical significance. For some years, however, pædiatricians have received much help from the application of this test, first of all in infancy and latterly in the older child and adolescent.

That the incidence of tuberculosis is becoming less in enlightened communities is an established fact. That many persons attain adult life without having become infected by the tubercle bacillus is also well known. In many districts this reduction in infection probably has resulted from intensification of our campaign against tuberculosis and improved living conditions. Table I demonstrates the results that have been obtained amongst school children at the Royal Edward Institute. The same supervision and, to a large extent, the same group of nurses have

TABLE I.

ROYAL EDWARD INSTITUTE
CONTACT CLINIC FOR CHILDREN

Year	*Number given Mantoux tests*	*Positive reactions*	*Positive percentage*	*Number of consultations*
1933	726	415	57.0	2,178
1934	706	351	49.5	3,147
1935	738	316	42.8	2,854
1936	732	316	43.1	2,700
1937	556	185	33.3	2,284
1938	678	232	34.2	2,089
1939	808	270	33.4	2,588
Totals	4,944	2,085		17,840

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